

CLAIMS

1. A variant of FVII or FVIIa, wherein said variant comprises at least one amino acid modification in a position selected from the group consisting of 196, 237 and 341 as compared to hFVII or hFVIIa (SEQ ID NO:2).
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2. The variant of claim 1, wherein said variant is a variant of hFVIIa.
3. The variant of claim 1 or 2, wherein said variant comprises a modification in position 196 as compared to hFVII or hFVIIa (SEQ ID NO:2).
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4. The variant of claim 3, wherein said modification is a substitution.
5. The variant of claim 4, wherein said substitution is D196K or D196N.
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6. The variant of claim 1 or 2, wherein said variant comprises a modification in position 237 as compared to hFVII or hFVIIa (SEQ ID NO:2).
7. The variant of claim 6, wherein said modification is a substitution.
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8. The variant of claim 7, wherein said substitution is G237L.
9. The variant of claim 6, wherein said modification is an insertion.
- 25 10. The variant of claim 9, wherein said insertion is selected from the group consisting of G237GXX, G237GXXX and G237GXXXX, wherein X is any amino acid residue.
11. The variant of claim 10, wherein X is selected from the group consisting Ala, Val, Leu, Ile, Gly, Ser and Thr.
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12. The variant of claim 11, wherein X is Ala.
13. The variant of claim 12, wherein said insertions are G237GAA.

14. The variant of claim 1 or 2, wherein said variant comprises a modification in position 341 as compared to hFVII or hFVIIa (SEQ ID NO:2).

15. The variant of claim 14, wherein said modification is a substitution.

16. The variant of claim 15, wherein said substitution is K341Q.

17. The variant of any of claims 1-16, wherein said variant comprises 1-10 further amino acid modifications.

18. The variant of claim 17, wherein said further modifications are substitutions.

19. The variant of claim 17 or 18, wherein at least one of said further amino acid substitutions is made in the Gla domain.

20. The variant of claim 19, comprising at least one further substitution in a position selected from the group consisting of P10, K32, D33 and A34, and an insertion between A3 and F4.

21. The variant of claim 20, comprising a further substitution in position K32.

22. The variant of claim 21, wherein said further substitution is K32E.

23. The variant of any of claims 19-22, comprising a further substitution in position P10.

24. The variant of claim 23, wherein said further substitution is P10Q.

25. The variant of any of claims 19-24, comprising further substitutions in P10+K32+D33+A34 as well as insertion of an amino acid residue between A3 and F4.

26. The variant of claim 25, comprising the modifications A3AY+P10Q+K32E+D33F+A34E.

27. The variant of any of claims 19-26, wherein no modifications are made in residues 6, 7, 14, 16, 19, 20, 25, 26, 29 and 35.

28. The variant of any of claims 1-27, wherein at least one amino acid residue comprising an attachment group for a non-polypeptide moiety has been introduced or removed.

5 29. The variant of claim 28, wherein at least one amino acid residue comprising an attachment group for a non-polypeptide moiety has been introduced.

30. The variant of claim 29, wherein at least one non-polypeptide moiety is covalently attached to at least one of said attachment groups.

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31. The variant of claim 30, wherein said attachment group is a glycosylation site.

32. The variant of claim 31, wherein said non-polypeptide moiety is a sugar moiety.

15 33. The variant of claim 31 or 32, wherein the introduced glycosylation site is an *in vivo* glycosylation site.

34. The variant of claim 33, wherein the *in vivo* glycosylation site is an *in vivo* O-glycosylation site.

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35. The variant of claim 33, wherein the *in vivo* glycosylation site is an *in vivo* N-glycosylation site.

36. The variant of claim 35, wherein said *in vivo* N-glycosylation site is introduced into a
25 position comprising an amino acid residue having at least 25% of its side chain exposed to the surface (as defined in Example 1 herein).

37. The variant of claim 36, wherein said *in vivo* N-glycosylation site is introduced into a
30 position comprising an amino acid residue having at least 50% of its side chain exposed to the surface (as defined in Example 1 herein).

38. The variant of any of claims 35-37, wherein said *in vivo* N-glycosylation site is introduced by at least one substitution selected from the group consisting of A51N, G58N, T106N, K109N, G124N, K143N+N145T, A175T, I205S, I205T, V253N, T267N,

T267N+S269T, S314N+K316S, S314N+K316T, R315N+V317S, R315N+V317T, K316N+G318S, K316N+G318T, G318N and D334N.

39. The variant of claim 38, wherein said *in vivo* N-glycosylation site is introduced by at least
5 one substitution selected from the group consisting of A51N, G58N, T106N, K109N, G124N, K143N+N145T, A175T, I205T, V253N, T267N+S269T, S314N+K316T, R315N+V317T, K316N+G318T, G318N and D334N.

40. The variant of claim 39, wherein said *in vivo* N-glycosylation site is introduced by at least
10 one substitution selected from the group consisting of T106N, A175T, I205T, V253N and T267N+S269T.

41. The variant of any of claims 35-40, wherein one *in vivo* N-glycosylation site has been introduced by substitution.

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42. The variant of any of claims 35-40, wherein two or more *in vivo* N-glycosylation sites have been introduced by substitution.

43. The variant of claim 42, wherein two *in vivo* N-glycosylation sites have been introduced
20 by substitution.

44. The variant of claim 42 or 43, wherein said *in vivo* N-glycosylation sites have been introduced by substitutions selected from the group consisting of A51N+G58N, A51N+T106N, A51N+K109N, A51N+G124N, A51N+K143N+N145T, A51N+A175T, A51N+I205T, A51N+V253N, A51N+T267N+S269T, A51N+S314N+K316T, A51N+R315N+V317T, A51N+K316N+G318T, A51N+G318N, A51N+D334N, G58N+T106N, G58N+K109N, G58N+G124N, G58N+K143N+N145T, G58N+A175T, G58N+I205T, G58N+V253N, G58N+T267N+S269T, G58N+S314N+K316T, G58N+R315N+V317T, G58N+K316N+G318T, G58N+G318N, G58N+D334N, T106N+K109N, T106N+G124N, T106N+K143N+N145T, T106N+A175T, T106N+I205T, T106N+V253N, T106N+T267N+S269T, T106N+S314N+K316T, T106N+R315N+V317T, T106N+K316N+G318T, T106N+G318N, T106N+D334N, K109N+G124N, K109N+K143N+N145T, K109N+A175T, K109N+I205T, K109N+V253N, K109N+T267N+S269T, K109N+S314N+K316T, K109N+R315N+V317T,

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K109N+K316N+G318T, K109N+G318N, K109N+D334N, G124N+K143N+N145T,
 G124N+A175T, G124N+I205T, G124N+V253N, G124N+T267N+S269T,
 G124N+S314N+K316T, G124N+R315N+V317T, G124N+K316N+G318T, G124N+G318N,
 G124N+D334N, K143N+N145T+A175T, K143N+N145T+I205T, K143N+N145T+V253N,
 5 K143N+N145T+T267N+S269T, K143N+N145T+S314N+K316T,
 K143N+N145T+R315N+V317T, K143N+N145T+K316N+G318T, K143N+N145T+G318N,
 K143N+N145T+D334N, A175T+I205T, A175T+V253N, A175T+T267N+S269T,
 A175T+S314N+K316T, A175T+R315N+V317T, A175T+K316N+G318T, A175T+G318N,
 A175T+D334N, I205T+V253N, I205T+T267N+S269T, I205T+S314N+K316T,
 10 I205T+R315N+V317T, I205T+K316N+G318T, I205T+G318N, I205T+D334N,
 V253N+T267N+S269T, V253N+S314N+K316T, V253N+R315N+V317T,
 V253N+K316N+G318T, V253N+G318N, V253N+D334N, T267N+S269T+S314N+K316T,
 T267N+S269T+R315N+V317T, T267N+S269T+K316N+G318T, T267N+S269T+G318N,
 T267N+S269T+D334N, S314N+K316T+R315N+V317T, S314N+K316T+G318N,
 15 S314N+K316T+D334N, R315N+V317T+K316N+G318T, R315N+V317T+G318N,
 R315N+V317T+D334N and G318N+D334N.

45. The variant of claim 44, wherein said *in vivo* N-glycosylation sites have been introduced
 by substitutions selected from the group consisting of T106N+A175T, T106N+I205T,
 20 T106N+V253N, T106N+T267N+S269T, A175T+I205T, A175T+V253N,
 A175T+T267N+S269T, I205T+V253N, I205T+T267N+S269T and V253N+T267N+S269T.

46. The variant of claim 45, wherein said *in vivo* N-glycosylation sites have been introduced
 by substitutions selected from the group consisting of T106N+I205T, T106N+V253N and
 25 I205T+T267N+S269T.

47. The variant of any of claims 35-40, wherein three or more *in vivo* N-glycosylation sites
 have been introduced by substitution.

30 48. The variant of claim 47, wherein three *in vivo* N-glycosylation sites have been introduced
 by substitution.

49. The variant of claim 47 or 48, wherein said *in vivo* N-glycosylation sites have been introduced by substitutions selected from the group consisting of I205T+V253N+T267N+S269T and T106N+I205T+V253N.

5 50. The variant of any of the preceding claims, wherein said variant further comprises at least one modification in a position selected from the group consisting of 157, 158, 296, 298, 305, 334, 336, 337 and 374.

51. The variant of claim 50, wherein said modification is at least one substitution selected
10 from the group consisting of V158D, E296D, M298Q, L305V and K337A.

52. The variant of claim 51, wherein said substitutions are selected from the group consisting of V158D+E296D+M298Q+L305V+K337A,
V158D+E296D+M298Q+K337A, V158D+E296D+M298Q+L305V,
15 V158D+E296D+M298Q, M298Q, L305V+K337A, L305V and K337A.

53. The variant of any of the preceding claims, wherein said variant further comprises at least one modification selected from the group consisting of L39E, L39Q, L39H, I42R, S43H, S43Q, K62E, K62R, L65Q, L65S, F71D, F71Y, F71E, F71Q, F71N, E82Q, E82N, E82K and
20 F275H.

54. The variant of any of the preceding claims, wherein said variant is in its activated form.

55. A nucleotide sequence encoding a variant as defined in any of claims 1-54.
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56. An expression vector comprising a nucleotide sequence as defined in claim 55.

57. A host cell comprising a nucleotide sequence as defined in claim 55 or an expression vector as defined in claim 56.
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58. The host cell of claim 57, wherein said host cell is a gamma-carboxylating cell capable of *in vivo* glycosylation.

59. A composition comprising a variant as defined in any of claims 1-54 and at least one pharmaceutically acceptable carrier or excipient.

60. A variant as defined in any of claims 1-54 for use as a medicament.

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61. Use of a variant as defined in any of claims 1-54 for the manufacture of a medicament for the treatment of a disease or a disorder wherein clot formation is desirable.

62. Use according to claim 61, wherein said disease or disorder is selected from the group
10 consisting of hemorrhages, including brain hemorrhages, severe uncontrolled bleedings, such as trauma, bleedings in patients undergoing transplantations or resection, variceal bleedings, and hemophilia.

63. Use according to claim 62, wherein said disease or disorder is trauma.

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64. Use according to claim 62, wherein said disease or disorder is hemophilia.

65. A method for treating a mammal having a disease or a disorder wherein clot formation is desirable, comprising administering to a mammal in need thereof an effective amount of the
20 variant as defined in any of claims 1-54 or the composition of claim 59.

66. The method of claim 65, wherein said disease or disorder is selected from the group consisting of hemorrhages, including brain hemorrhages, severe uncontrolled bleedings, such as trauma, bleedings in patients undergoing transplantations or resection, variceal bleedings,
25 and hemophilia.

67. The method of claim 66, wherein said disease or disorder is trauma.

68. The method of claim 66, wherein said disease or disorder is hemophilia.

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